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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,313	06/03/2002	Michael Hallek	50125/044001	5985

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EXAMINER	
CHEN, STACY BROWN	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 08/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/031,313	HALLEK ET AL.	
	Examiner	Art Unit	
	Stacy B. Chen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *74,77-80 and 82-93* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *74,77-80 and 82-93* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 21, 2005 has been entered. Claims 74, 77-80 and 82-93 are under examination.

2. The previous rejection of claims 74-93 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention is moot with regard to cancelled claims 75-76 and 81, and withdrawn with regard to claims 74, 77-80 and 82-93 in view of Applicant's amendments.

3. The rejection of claims 74, 75, 79, 80-85 and 92 under 35 U.S.C. 112, first paragraph, for being enabling for a method for reducing antigenicity of adeno-associated virus (AAV) comprising modifying the capsid (VP), but not enabled for reducing antigenicity of AAV comprising the modification of any structural protein, is withdrawn in view of Applicant's amendment, and moot in view of cancelled claims 75 and 81.

Oath/Declaration

4. The Office has located the originally signed oath/declaration filed June 3, 2002. It is noted that Applicant indicated in the response filed June 21, 2005 that a copy of that declaration was filed concurrently, however, no copy was entered into the application. Regardless, the originally signed declaration is acknowledged and there is no need for another copy.

Claim Rejections - 35 USC § 112

5. (*New rejection*) Claims 74, 77-80 and 82-93 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- The claims recite, "reducing the antigenicity of an AAV particle". The metes and bounds of the method cannot be determined without a definition of reduced antigenicity. How does one measure the reduced antigenicity? One of skill in the art would not know how to detect reduced antigenicity without further explanation in the form of additional method steps with clear endpoints for "reduction".
- Claim 89 is referring to nucleic acid when the new limitation, "comprising 72 amino acids" is recited. The metes and bounds of the claim cannot be determined lacking a clear reference to nucleic acids or amino acids deletions having "62".
- Claims 92 and 93 recite limitations that are seemingly redundant with the claims from which they depend, claims 74 and 85. Claim 74 indicates that the modification takes place in the VP1, VP2, or VP3 region. These regions *are* the capsid. If Applicant's intent was to broaden claims 92 and 93, then that is also indefinite. A broad range or

limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Clarification and correction are required.

6. (*New rejection*) Claims 74, 77-80, 82-90, 92 and 93 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are drawn to a method of reducing the antigenicity of an AAV particle, wherein the modifications to the VP1-3 include a large genus of modifications. The claims encompass any modification (deletion, substitution, replacement, addition, etc.) at any point in the VP1-3 regions. Applicant has not adequately described the types of modifications such that the large genus is sufficiently provided for.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the factors present in the claims are a partial structure to which the modification is made, and a functional result: reduced antigenicity, particle formation ability and infectivity. Reduced antigenicity is indefinite (see

112, second paragraph rejection above). Even if the definition of reduced antigenicity were clear, the large genus of modifications needs to be further specified. There is no identification of any particular portion of the VP1-3 structure that must be conserved when making the modifications such that only reduced antigenicity is achieved or particle formation and infectivity retained. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Claim Rejections - 35 USC § 102

7. Claims 74, 77-80 and 82-93 remain rejected under 35 U.S.C. 102(b) as being anticipated by Mamounas *et al.* (WO 97/38723, herein, "Mamounas") for reasons of record. The claims as amended are drawn to a method for reducing the antigenicity of AAV comprising modifying AAV VP1, VP2 or VP3 in such a way as to bring about reduction in the antigenicity of AAV virus, and maintain particle formation and infectivity.

The teachings of Mamounas are reiterated for convenience. Mamounas discloses a capsid protein (structural protein) of AAV-2 that has been deleted (modified) in the VP1 or VP3 region (Example 1, pages 60-61, bridging paragraph, and page 67, part C). The deletion results in reduced specificity of the virus for the AAV receptor (page 4, lines 22-26), which is a reduction of the antigenicity of the virus for its natural receptor. Mamounas modifications of the VP1, VP2 and VP3 genes include the end of the AAV capsid gene open reading frame, and the start codon of the individual capsid genes (page 67, lines 13-22). Anti-CD34 scFv sequence was ligated to the 5' end of the VP1, VP2, and VP3 sequences using HindIII and NotI sites (page 67,

lines 21-26). Some of the insertions occur in the XhoI and XbaI cleavage sites (page 67, lines 21-23). Mamounas also teaches deleting a region of the VP1 or VP3 region and inserting a targeting ligand, which is an additional modification (page 4, lines 28-31). Antibodies, such as single chain variable region fragments, biotin, poly-L-lysine, transferrin, and other proteins are contemplated by Mamounas for integration into the VP regions (pages 30-32). Mamounas does not explicitly say that the insertion occurs between the BsrBI/HindII cleavage sites of the VP-1 encoding nucleic acid, however, since insertions occurred in the XhoI cleavage site, the insertions would be expected to take place somewhere within the BsrBI/HindII cleavage site because BsrBI/HindII cleavage sites are within the XhoI cleavage site. Regarding claim 91, which has the limitation of specific locations of insertions in VP3, the claims only require that the insertion be located before and/or after at least one amino acid in a sequence. Given that the claims only require that the insertion be before or after an amino acid, one would expect that the insertions by Mamounas would have occurred before or after an amino acid. Therefore, the claims are anticipated by Mamounas.

Applicant's arguments have been carefully considered but fail to persuade. Applicant's substantive arguments are primarily drawn to the assertion that Mamounas' AAV vector's structural protein is incapable of supporting viral particle formation. Applicant points to pages 67-68, where Mamounas discloses that an antibody-AAV construct (scFv-AAV capsid chimera) failed to produce any intact viral particles. Applicant argues that since Mamounas had to use a triple plasmid strategy to get intact viral particles, that Mamounas fails to teach the claimed invention.

In response to these arguments, the method uses the term, "comprising", rendering it open to including any number of additional steps. Mamounas' method does what Applicant's method does, with the additional steps of a triple-plasmid strategy in order to get an intact particle. In response to the argument that Mamounas' wild type capsid was responsible for particle formation, the instant claims do not limit the particle-formation ability to the modified capsid. Mamounas' capsid (VP) is modified (pVP-scFv, page 68), and it has a helper vector encoding the wild type capsid. Mamounas' method results in the same product, but with additional steps. The open claim language does not preclude the steps taken by Mamounas.

Further, the modifications made by Mamounas are the same as those claimed by Applicant. Applicant is arguing that those changes do not result in an intact particle and infectivity. If these assertions were true, then Applicant's invention would theoretically also be incapable of particle formation and infectivity. Clarification is requested regarding Applicant's argument that Mamounas' method, which contains the same elements as Applicant's claims, does not work.

Conclusion

8. No claim is allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James C. Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Stacy B. Chen
August 24, 2005